AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

Please replace the paragraph starting on page 7, line 7, with the following paragraph:

The protein databank (Brookhaven Protein Databank~~, http://www.rcsb.org/pdb/~~) currently indicates that there are 76 separate crystal structures available for the eight crystallized P450s, plus 7 crystal structures on hold (Sep. 1, 2002), the majority of which containing either bound substrates or inhibitors. Table 1 provides the relevant information about the structural templates used for human CYP3A model rebuilding. The idea behind homology modeling is that proteins belonging to the same functional class and showing a strong sequence identity, adopt a similar fold (review in (Hilbert et al. 1993)). Known analogous structures are then used to generate a template or parent structure for the unknown protein to be modeled. The reliability of the various methods employed depend mostly on the number of experimental 3D structures that can be aligned. Knowing that for pairs of distantly related proteins (with residue identity of about 20%) the regions having the same fold will represent less than half of each molecule, the regions where the folds differ will predominate, and the divergence of sequence must be compensated by a higher number of homologous proteins to align (Chothia and Lesk 1986). Below 50% of sequence identity, the deviation in structurally not conserved regions becomes significant, and loop regions are difficult to predict. It is generally accepted that below 20% of sequence identity, the prediction turns out to be hazardous, and fold assignment methods are best replaced by ab inilio methods, that ideally attempt to predict the native structure only from the primary sequence of the protein to

be modeled. But produced models so far had the correct fold for only a few small protein domains (Sanchez et al. 2000).

Please replace the paragraph starting on page 9, line 1, with the following paragraph:

Table 2: Sequence identities between the various crystallized cytochrome P450s and human CYP3A4 and CYP3A7 using BLOSUM 62 matrix (source LALIGN, ~~http://www.infobiogen.fr/services/analyseq/cgi-bin/lfastap_in.pl,~~ algorithm of Huang and Miller LALIGN that finds the best local alignments between two sequences, version 2.1u03 April 2000, published in Adv. Appl. Math. 1991, 12: 373-381). The P450 BM3 structure, Swissprot code name CPXB_BACME, corresponds to the structure of a fusion protein of P450 and a reductase domain, so that it displays twice the number of residues.